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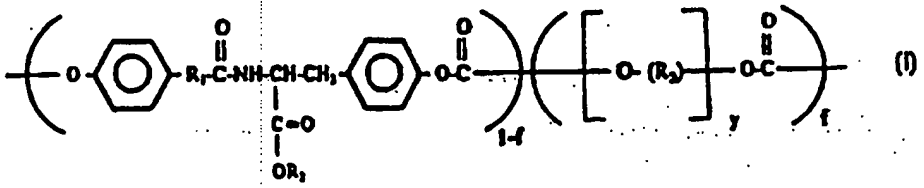
(54) Title: COPOLYMERS OF TYROSINE-BASED POLYCARBONATE AND POLY(ALKYLENE OXIDE)



(I)

(57) Abstract

Random block copolymers having formula (I), wherein R_1 is -CH=CH- or $(-CH_2-)_j$, in which j is zero or an integer from one to eight; R_2 is selected from hydrogen, straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms and derivatives or biologically and pharmaceutically active compounds covalently bonded to said copolymer; each R_3 is independently an alkylene group containing up to 4 carbon atoms; y is an integer between about 5 and about 3000; and f is the percent molar fraction of alkylene oxide in the copolymer and ranges between about 1 and about 99 mole percent. Implantable medical devices and drug delivery implants containing the random block copolymers are also disclosed, along with methods for drug delivery and for preventing the formation of adhesions between injured tissues employing the random block copolymers. Polyarylate random block copolymers are also described.

DESCRIPTION

COPOLYMERS OF TYROSINE-BASED POLYCARBONATE AND POLY(ALKYLENE OXIDE)

TECHNICAL FIELD

The present invention relates to copolymers of tyrosine-based polycarbonates and poly(alkylene oxide) and to methods of synthesizing such polymers.

BACKGROUND ART

Linear aromatic polycarbonates derived from diphenols such as bisphenol-A represent an important class of condensation polymers. Such polycarbonates are strong, tough, high melting materials. They are well-known in the literature and are commercially produced in large quantities.

The early investigations on block copolymers of poly(bisphenol-A carbonate) and poly(alkylene oxide) started in 1961 and were conducted by the groups of Merrill and Goldberg. Merrill, J. Polym. Sci., 55, 343-52 (1961) for the first time introduced poly(alkylene oxide) blocks into poly(bisphenol-A carbonate). Merrill described the interfacial copolymerization of poly(bisphenol-A carbonate) (dissolved in methylene chloride) and poly(alkylene oxide) bischloroformate (dissolved in aqueous sodium hydroxide). The presence of flexible blocks of poly(alkylene oxide) promoted the crystallization of the polycarbonate, which resulted in flexible polymers with high melting points. Later on, Goldberg, J. Polym. Sci., Part C, 4, 707-30 (1964) reported more work on block copolymers of poly(bisphenol-A carbonate) and poly(ethylene oxide). The incorporation of flexible, polar, water soluble block segments into the rigid, linear, aromatic polycarbonate chains produced elastomers with unusual thermal and plastic properties. In particular Goldberg described the use of poly(ethylene oxide) as a comonomer with bisphenol-A. The synthesis was based on the reaction of phosgene with the mixture of monomers in pyridine followed by purification of the copolymer by precipitation in isopropanol. Copolymers were studied for structure-property correlations as a function of

U.S. Patent Nos. 5,198,507 and 5,216,115 disclosed tyrosine-derived diphenolic monomers, the chemical structure of which was designed to be particularly useful in the polymerization of polycarbonates, polyiminocarbonates and polyarylates. The resulting polymers are useful as degradable polymers in general, and as tissue compatible bioerodible materials for biomedical uses in particular. The suitability of these polymers for this end-use application is the result of their derivation from naturally occurring metabolites, in particular, the amino acid L-tyrosine.

Tyrosine-based polycarbonates are strong, tough, hydrophobic materials that degrade slowly under physiological conditions. For many medical applications such as drug delivery, non-thrombogenic coatings, vascular grafts, wound treatment, artificial skin, relatively soft materials are needed that are more hydrophilic and degrade faster than the available tyrosine-based polycarbonates.

SUMMARY OF THE INVENTION

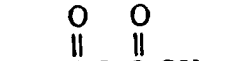
In this invention, the introduction of poly(alkylene oxide) segments into the backbone of tyrosine-based polycarbonates was found to lead to softer, more hydrophilic polymers that exhibited significantly increased rates of degradation. Since the previously known block copolymers of poly(bisphenol-A carbonate) and poly(alkylene oxide) apparently do not degrade appreciably under physiological conditions, the finding was unexpected that the incorporation of poly(alkylene oxide) into tyrosine-based polycarbonate significantly increased the rate of degradation. Furthermore, the disclosed copolymers of tyrosine-based polycarbonate and poly(ethylene oxide) have an alkyl ester pendent chain at each monomeric repeat unit. This pendent chain is an unprecedented structural feature among the currently known block copolymers of poly(bisphenol A carbonate) and poly(alkylene oxide). As shown in more detail below, variation in the length of the pendent chain can be used to fine-tune the polymer properties. Studies of this kind are known in the literature for other polymer systems, but have not been performed for block copolymers of poly(bisphenol A carbonate) and

acid) derived copolymers as described by Annaka et al., Nature, 355, 430-32 (1992); Tanaka et al., Phys. Rev. Lett., 45(20), 1636-39(1980) and Hirokawa et al., J. Chem. Phys., 81(12), 6379-80(1984), and poly(ethylene glycol)-poly(propylene glycol) copolymers as described by Armstrong et al., Macromol. Reports, A31(suppl. 6&7), 1299-306(1994). Polymer gels and solutions of these polymers are known to undergo continuous or discontinous volume change upon changes in temperature, solvent composition, pH or ionic composition. The driving forces for the phase change can be attractive or repulsive electrostatic interactions, hydrogen bonding or hydrophobic effects.

For nonionic synthetic polymers such as protein-based bioelastic materials, poly(N-isopropylacrylamide) and poly(ethylene glycol)-poly(propylene glycol) copolymers, as well as the copolymers of the present invention, the driving force of phase transition is the combination of hydrogen bonding and hydrophobic effect. As the temperature increases, the gels of these polymers undergo a phase transition from a swollen to a collapsed state, while polymer solutions precipitate at certain temperature or within certain temperature ranges. These polymers, including the copolymers of the present invention, and especially those that undergo a phase transition at about 30-40°C on heating can be used as biomaterials for drug release and clinical implantation materials. Specific applications include the prevention of adhesions and tissue reconstruction.

Therefore, the present invention also includes implantable medical devices containing the random block copolymers of the present invention. In one embodiment of the present invention, the copolymers are combined with a quantity of a biologically or pharmaceutically active compound sufficient for therapeutically effective site-specific or systemic drug delivery as described by Gutowska et al., J. Biomater. Res., 29, 811-21 (1995) and Hoffman, J. Controlled Release, 6, 297-305 (1987). In another embodiment of the present invention, the copolymer is in the form of a sheet or a coating applied to exposed

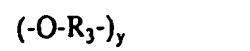
the dicarboxylic acid has the structure of Formula III:



(III)

in which R is selected from saturated and unsaturated, substituted and unsubstituted alkyl, aryl, and alkylaryl groups containing up to 18 carbon atoms; and

the poly(alkylene oxide) has the structure of Formula IV:



(IV)

in which each R_3 is independently selected from alkylene groups containing up to 4 carbon atoms and y is between about 5 and about 3000.

Copolymers based on tyrosine-derived diphenols and poly(alkylene oxide) represent a new group of nonionic polymers that show inverse temperature transitions. These copolymers contain natural amino acids as building blocks, are degradable under physiological conditions, and have been shown to be biocompatible. By changing the tyrosine-derived diphenol, the poly(alkylene oxide) and the ratio of the two components, the copolymers can be designed and synthesized to exhibit desired transition temperatures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the glass transition temperatures of poly(DTE co $PEG_{1,000}$ carbonates) (O), poly(DTB co $PEG_{1,000}$ carbonates) (Δ) and poly(DTH co $PEG_{1,000}$ carbonates) (◊) of the present invention having different PEG contents and in comparison to corresponding polycarbonate homopolymers;

FIG. 2 depicts the water uptake of poly(DTE co 5% $PEG_{1,000}$ carbonate) (o), poly(DTE co 15% $PEG_{1,000}$ carbonate) (◊) and poly(DTE co 30% $PEG_{1,000}$ carbonate) (Δ) measured as a function of incubation time at 37°C in phosphate buffered saline;

FIG. 3 depicts the pNA release from poly(DTB carbonate) (O), poly(DTB co 1% $PEG_{1,000}$ carbonate) (Δ) and poly(DTB co 5% $PEG_{1,000}$ carbonate) (◊) microspheres measured as a function of incubation time at 37°C in phosphate buffer;

octyl group. When R_1 is $-CH_2-CH_2-$, the diphenol compound of Formula I is referred to as a desaminotyrosyl-tyrosine alkyl ester. The most preferred member of the group of desaminotyrosyl-tyrosine alkyl esters is the hexyl ester, referred to as desaminotyrosyl-tyrosine hexyl ester or DTH.

The diphenol compounds may be prepared as described in the above-referenced U.S. Patent Application Serial No. 08/414,339. The method described in U.S. Patent No. 5,099,060 may also be employed, and is incorporated herein by reference.

The poly(alkylene oxide) shown in Formula IV can be any commonly used alkylene oxide known in the art, as is preferably a poly(ethylene oxide), poly(propylene oxide) or poly(tetra methylene oxide). Poly(alkylene oxide) blocks containing ethylene oxide, propylene oxide or tetramethylene oxide units in various combinations are also possible constituents within the context of the current invention.

The poly(alkylene oxide) is most preferably a poly(ethylene oxide) in which y of Formula IV is between about 20 and about 200. More preferred embodiments are obtained when poly(ethylene oxide) blocks with a molecular weight of about 1,000 to about 20,000 g/mol are used. For these preferred embodiments, in the structure of Formula IV, both R_3 groups are hydrogen and y has values from about 22 to about 220. A value for y ranging between about 22 and about 182 is even more preferred.

The random block copolymers of Formula I may be prepared by the conventional methods for polymerizing diphenols into polycarbonates described in the aforementioned U.S. Patent No. 5,099,060, which methods are also incorporated herein by reference. This involves the reaction of the desired ratio of tyrosine-derived diphenol and poly(alkylene oxide) with phosgene or phosgene precursors (e.g., diphosgene or triphosgene) in the presence of a catalyst. Thus, the copolymers of Formula I may be prepared by interfacial polycondensation, polycondensation in a homogeneous phase or by transesterification. The suitable processes, associated catalysts and solvents are

cephalothin, melphalan, penicillin V, aspirin, nicotinic acid, chemodeoxycholic acid, chlorambucil, and the like. The compounds are covalently bonded to the copolymer or diphenol by methods well understood by those of ordinary skill in the art. Drug delivery compounds may also be formed by physically blending the biologically or pharmaceutically active compound to be delivered with the random block copolymers of the present invention using conventional techniques well-known to those of ordinary skill in the art.

The tyrosine-derived diphenol compounds of Formula II and the poly(alkylene oxide) of Formula IV may also be reacted according to the method disclosed by U.S. Patent No. 5,216,115 to form polyarylates, the disclosure of which is hereby incorporated by reference thereto. As disclosed by U.S. Patent No. 5,216,115, the diphenol compounds are reacted with the aliphatic or aromatic dicarboxylic acids of Formula III in a carbodiimide mediated direct polyesterification using 4-(dimethylamino)pyridinium-p-toluene sulfonate (DPTS) as a catalyst to form aliphatic or aromatic polyarylates. Random block copolymers with poly(alkylene oxide) may be formed by substituting poly(alkylene oxide) for the tyrosine derived diphenol compound in an amount effective to provide the desired ratio of diphenol to poly(alkylene oxide) in the random block copolymer. The random block copolymers of the present invention can be worked up by known methods commonly employed in the field of synthetic polymers.

INDUSTRIAL APPLICABILITY

A variety of useful articles with valuable physical and chemical properties may be derived from the random block copolymers of the present invention, which are based on tissue-compatible monomers. The useful articles can be shaped by conventional polymer-forming techniques such as extrusion, compression molding, injection molding, solvent casting, spin casting, and the like. Shaped articles prepared from the polymers are useful, inter alia, as degradable biomaterials for medical implant applications. Such applications include the use of the shaped articles as vascular grafts and stents, bone plates,

COMPRESSION MOLDING

Thin polymer films were prepared by compression molding. Processing temperature was 30-35°C above Tg for each polymer. To minimize polymer adhesion to the metal plates of the mold, two teflon sheets were added between the polymer and metal plates of the mold.

SPECTROSCOPY

FT-IR spectra were recorded on a Matson Cygnus 100 spectrometer. Polymer samples were dissolved in methylene chloride and films were cast directly onto NaCl plates. All spectra were collected after 16 scans at 2 cm^{-1} resolution. UV/Vis spectra were recorded on a Perkin-Elmer Lambda 3B spectrophotometer. NMR spectra of polymer solutions in deuterated chloroform were recorded on a Varian VXR-200 spectrometer (64 scans).

GEL PERMEATION CHROMATOGRAPHY (GPC)

The chromatographic system consisted of a Perkin-Elmer Model 410 pump, a Waters Model 410 RI detector, and a PE-Nelson Model 2600 computerized data station. Two PL-gel GPC columns (pore size 10^5 and 10^3 Å) were operated in series at a flow rate of 1 ml/min using THF. Molecular weights were calculated relative to polystyrene standards without further correction.

THERMAL ANALYSIS

The glass transition temperature (T_g) was determined by differential scanning calorimetry (DSC) on a DuPont 910 DSC instrument calibrated with indium. Each specimen was subjected to two consecutive DSC scans. After the first run the specimen was quenched with liquid nitrogen and the second scan was performed immediately thereafter. T_g was determined in the second DSC scan as the midpoint. The heating rate for all polymers was 10°C/min and the average sample size was 10 mg.

WATER UPTAKE

A piece of copolymer (15-20 mg) was cut from a film incubated in PBS at 37°C, and wiped to remove water on the surface of the sample. Water

extracted into aqueous phosphate buffer solution (0.1 M, pH 7.4) followed by florescence spectrophotometry (excitation: 495 nm, emission: 520 nm).

An exactly weighed amount of pNA or FITC-dextran loaded microspheres were placed in an exactly measured volume of phosphate buffer solution (0.1 M, pH 7.4) at 37°C in a water shaker bath. The amount of pNA or FITC-dextran released into the buffer solution was determined as described above.

CELL GROWTH

Fetal rat lung fibroblasts (#CCL192, American Tissue Culture Collection) were grown in Ryan Red medium with 50 mg/ml sodium ascorbate and 10% fetal calf serum as described by Poiani et al., Amino Acids, 4, 237-48 (1993) and Ryan et al., J. Tiss. Cult. Meth., 10, 3-5 (1986). For polymer evaluation, the dual chamber units (#177380, Nunc, Inc.) were spin cast first with a styrene silane copolymer solution (2.5% w/v in ethyl acetate), which served as a coupling agent, and then with the polymer solution of interest. Unmodified plastic (#177429, Nunc) and glass dual chamber units (#177380, Nunc) served as controls and were used as received. Prior to cell seeding, all surfaces were incubated for 3 hours with PBS containing 5% penicillin-streptomycin. Cells from passage 5 were subsequently seeded at a density of 10^4 cells/cm^2. After 1 or 5 days of incubation, the cells were gently rinsed with PBS, and trypsinized from 3 separate chambers. The suspension was counted 4 times in a hemocytometer.

MEASUREMENT OF INVERSE TEMPERATURE TRANSITION

The detection of inverse phase transition is based on the increase in turbidity as the initial soluble polymerprecipitates upon heating. The increase in turbidity is monitored by visible spectroscopy as described below.

Polymer solutions: Optical Density (OD) measurements for 0.05% (w/v) polymer aqueous solutions were performed at 500 nm on a diode array spectrophotomer (Hewlett Packard, Model 8452-A) with a water-jacketed cell holder coupled with a refrigerated circulating bath (Neslab, model RTE-8).

weight of 127,000 daltons, a number average molecular weight of 84,000 daltons and a polydispersity of 1.5.

EXAMPLE 2

Poly(DTE co 30% $PEG_{1,000}$ carbonate) was synthesized as follows:

5.23 g of DTE (14.6 mmole) and 6.20 g of $PEG_{1,000}$ (6.27 mmole) were placed into a 250 ml flask. Then 60 ml of dry methylene chloride and 6.7 ml of anhydrous pyridine were added. At room temperature, 13.5 ml of a 1.93 M solution of phosgene in toluene was added slowly to the solution with overhead stirring during 90 minutes. 180 ml THF was added to dilute the reaction mixture. The copolymer was precipitated by slowly adding the mixture into 2400 ml of ethyl ether. The copolymer was redissolved in 200 ml THF (5% w/v solution) and reprecipitated by slowly adding the polymer solution into 2000 ml of water.

8.9 g of a white copolymer was obtained. As determined by GPC using THF as the solvent, the copolymer has a weight average molecular weight of 41,000 daltons, a number average molecular weight of 31,000 daltons and a polydispersity of 1.3.

EXAMPLE 3

Poly(DTO co 5% $PEG_{1,000}$ carbonate) was synthesized as follows:

9.23 g of DTO (20.9 mmole) and 1.09 g of $PEG_{1,000}$ (1.1 mmole) were placed into a 250 ml flask. Then 50 ml of dry methylene chloride and 7.0 ml of anhydrous pyridine were added. At room temperature, 14.3 ml of a 1.93 M solution of phosgene in toluene was added slowly to the solution with overhead stirring during 90 minutes. 150 ml THF was added to dilute the reaction mixture. The copolymer was precipitated by slowly adding the mixture into 2000 ml of ethyl ether. The copolymer was redissolved in 200 ml THF (5% w/v solution) and reprecipitated by slowly adding the polymer solution into 2000 ml of water.

70 ml THF (5% w/v solution) and reprecipitated by slowly adding the polymer solution into 700 ml of isopropanol.

6.4 g of a white copolymer was obtained. As determined by GPC using THF as the solvent, the copolymer has a weight average molecular weight of 47,000 daltons, a number average molecular weight of 37,000 daltons and a polydispersity of 1.3.

Poly(DTB co 1% $PEG_{1,000}$ carbonate), Poly(DTB co 5% $PEG_{1,000}$ carbonate), Poly(DTB co 10% $PEG_{1,000}$ carbonate), Poly(DTH co 1% $PEG_{1,000}$ carbonate), Poly(DTH co 5% $PEG_{1,000}$ carbonate), Poly(DTH co 10% $PEG_{1,000}$ carbonate), Poly(DTH co 20% $PEG_{1,000}$ carbonate) and poly(bisphenol-A co 5% $PEG_{1,000}$ carbonate) were synthesized by similar methods and used for different studies.

POLYMER CHARACTERIZATION

GLASS TRANSITION TEMPERATURE

Copolymers were prepared according to the examples given above. The glass transition temperature (T_g) of these copolymers and their corresponding polycarbonate homopolymers were measured (Fig.1). In each series of copolymers, T_g of the copolymers decreased as the molar fraction of $PEG_{1,000}$ increased.

MECHANICAL PROPERTIES

Tensile modulus: The dry specimens of poly(DTE co 5% $PEG_{1,000}$ carbonate) had tensile modulus of 1.3 Gpa, which is comparable to all tyrosine-derived polycarbonates which have tensile modulus within a range of 1.2-1.6 Gpa. See Ertel et al., J. Biomed. Mater. Res., 28, 919-930 (1994). After 24 h of incubation, the specimens had 10% of water uptake, and the tensile modulus dropped to 0.58 Gpa.

Tensile strength at yield and break: The combination of PEG into the backbone of the tyrosine derived polymer had a profound effect on the tensile strength and ductility of the polymer. While poly(DTE carbonate) was very brittle and failed without yielding after 4% elongation (See the aforementioned

carbonate). For poly(DTB co 10%PEG_{1000} carbonate), no microspheres could be isolated.

It was an unexpected finding that the presence of even very small molar fractions of poly(alkylene oxide) had a significant effect on the drug release rate. This is illustrated in Fig. 3, showing the cumulative release of pNA from the series of copolymers of DTB and PEG_{1000}.

The release of FITC-dextran from microspheres made of the homopolymers was extremely slow. The typical release profile for FTIC-dextran from the homopolymers was characterized by a short burst effect followed by a very long lag period during which no further FITC-dextran was released from the microspheres. Including 1 to 5% of $PEG_{1.000}$ in the polymer composition led to a significant increase in the amount of FITC-dextran that was rapidly released from the microspheres (Fig. 4). Thus, the disclosed copolymers can assist in the formulation of controlled drug release systems for hydrophilic, high molecular weight drugs.

DEGRADATION IN VITRO

Degradation study was performed for two poly(DTE co $PEG_{1.000}$ carbonates) with poly(bisphenol-A co 5% $PEG_{1.000}$ carbonate) as control. After one day of incubation in buffer at 37°C, thin film specimens of all copolymers had adsorbed water and reached saturation. Contrary to the industrially used very slowly degrading poly(bisphenol-A co PEG carbonates) the tyrosine-derived poly(DTX co PEG carbonates) degraded fast under physiological conditions in vitro, as demonstrated by GPC.

The changes in the molecular weight over time were followed for all three polymers. When the changes were plotted as percent molecular weight retention vs. time, all three polymers had similar degradation profiles, shown for poly(bisphenol-A co 5% $PEG_{1.000}$ carbonate), poly(DTE co 5% $PEG_{1.000}$ carbonate) and poly(DTE co 30% $PEG_{1.000}$ carbonate) in Fig. 5. During nine weeks of observation, poly(bisphenol-A co 5% $PEG_{1.000}$ carbonate) lost only about 15% of its molecular weight while poly(DTE co 5% $PEG_{1.000}$ carbonate)

Table I

Cell Attachment And Proliferation On Surfaces Of Copolymers			
PEG Copolymer		Attachment	Proliferation
Diphenol	Mole%PEG	(X100 cells/cm^2)	
		1 day	5 days
DTE	0	46± 13	596± 100
	5	8± 8	46± 14
	15	4± 5	11± 10
	30	3± 5	11± 10
DTB	0	56± 17	401± 79
	1	50± 14	163± 40
	5	16± 10	18± 13
	10	9± 9	7± 7
DTH	0	32± 10	268± 46
	1	52± 31	275± 71
	5	9± 11	3± 7
	10	9± 11	11± 14
Control surfaces			
glass		50± 16	555± 91
poly(BPA carbonate)		17± 10	123± 37

The foregoing examples and description of the preferred embodiment should be taken as illustrating, rather than as limiting, the present invention as defined by the claims. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. Such variations are not regarded as a departure from the spirit and scope of the invention, and all such modifications are intended to be included within the scope of the following claims.

7. The random block copolymer of claim 1, characterized in that f is between about 5 and about 95 mole percent.

8. An implantable medical device characterized by the random block copolymer of claim 1.

9. The implantable medical device of claim 8, characterized in that the surface of said device is coated with said random block copolymer.

10. The implantable medical device of claim 8, characterized by a biologically or physiologically active compound in combination with said random block copolymer, wherein said active compound is present in an amount sufficient for therapeutically effective site-specific or systemic drug delivery.

11. The implantable medical device of claim 10, characterized in that said biologically or physiologically active compound is covalently bonded to said copolymer.

12. An implantable medical device in the form of a sheet consisting essentially of the random block copolymer of claim 1 for use as a barrier for surgical adhesion prevention.

13. A method for site-specific or systemic drug delivery by implanting in the body of a patient in need thereof an implantable drug delivery device characterized by a therapeutically effective amount of a biologically or physiologically active compound in combination with the random block copolymer of claim 1.

14. The method of claim 13, characterized in that said biologically or physiologically active compound is covalently bonded to said copolymer.

15. A method for preventing the formation of adhesions between injured tissues characterized by inserting as a barrier between said injured tissues a sheet consisting essentially of the random block copolymer of claim 1.

16. A polyarylate, characterized by being polymerized as a random block copolymer of a dicarboxylic acid with both a tyrosine-derived

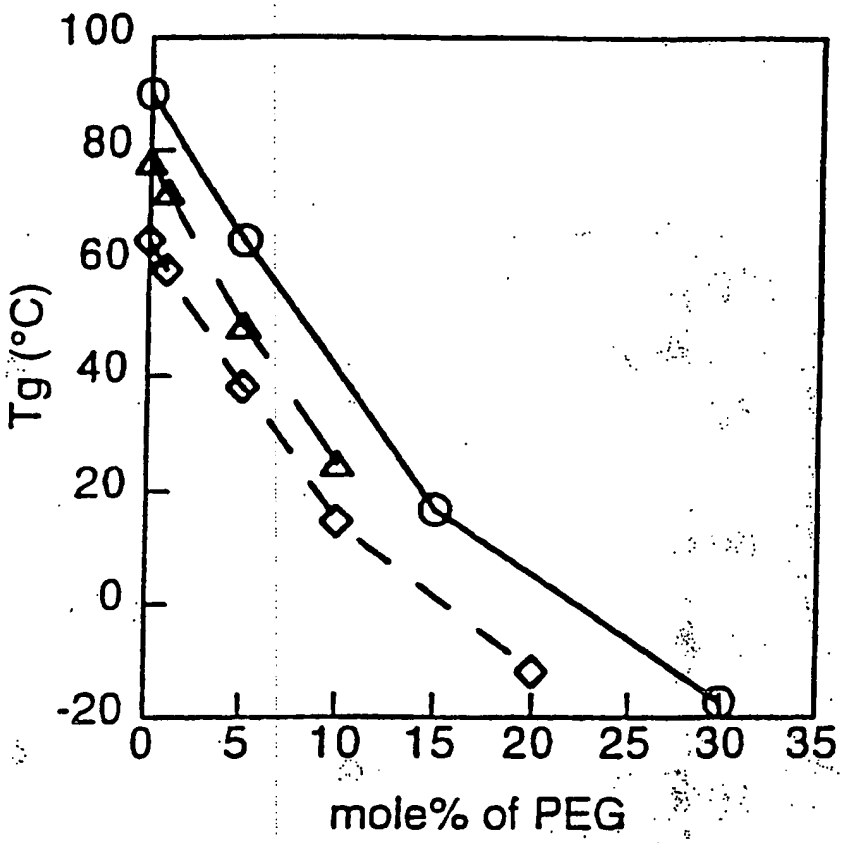


FIG. 1

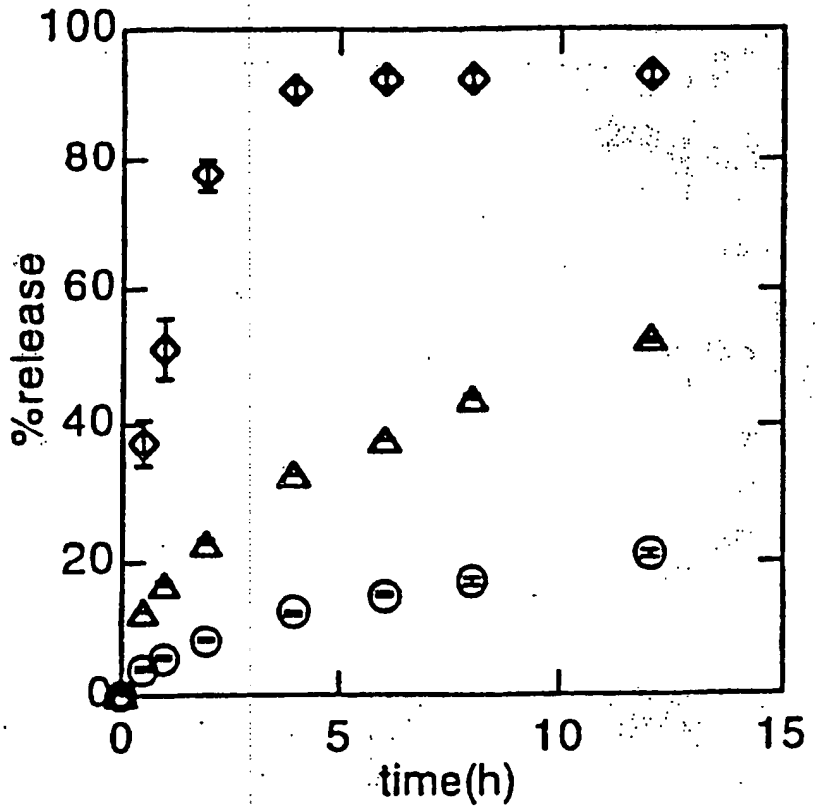


FIG.3

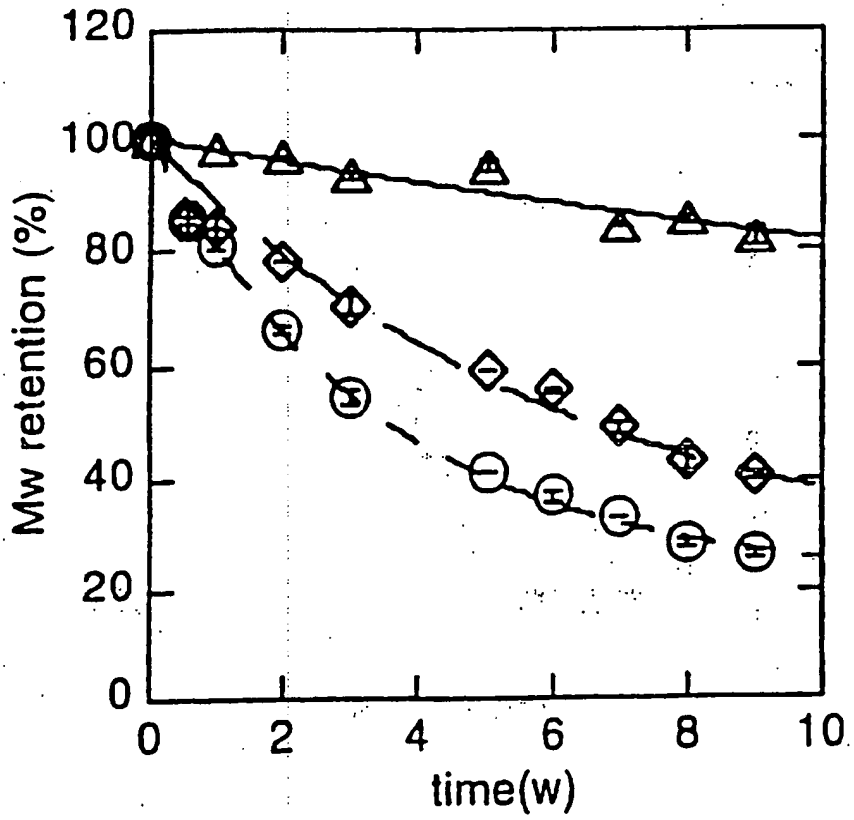


FIG.5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19098

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C08L 77/00; C08G 63/00, 64/00, 63/02, 69/26

US CL :525/432, 434; 528/176, 196, 272, 332

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 525/432, 434; 528/176, 196, 272, 332

C08L 77/00; C08G 63/00, 64/00, 63/02, 69/26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
03 A	US, A, 5,099,060 (KOHN ET AL.) 24 March 1992, column 3, line 7 through column 4, line 28.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 FEBRUARY 1997	26 MAR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer TERRESSA M. MOSLEY acp for Telephone No. (703) 308-1235

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